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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/393,173	09/09/99	CURIEL D	D6163

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EXAMINER	
CONNELL, Y	
ART UNIT	**PAPER NUMBER**
1633	5

DATE MAILED: 07/06/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/393,173	Curiel et al.
Examiner	**Group Art Unit**
Yvette Connell Albert	1633

☒ Responsive to communication(s) filed on *Apr 18, 2000* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-10* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-10* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION.

Response to Amendment

Applicant's amendment filed 4/18/00 (Paper No. 4) has been entered. Claim 4 has been canceled. Claims 1-3, and 5-10 have been amended and are currently pending in the present application.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-3 and 5-10 remain rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for making a vector encoding the bax gene and expressing the gene in tumor cells *in vitro*, does not reasonably provide enablement for administering a pharmacologically effective dose of this recombinant adenoviral vector therapy to treat any individual having a pathophysiological state. The specification does not enable any person skilled in the art or to which it most nearly pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, and is repeated for the same reasons of record as set forth in the Official action mailed 12/13/99.

Applicant's arguments filed 4/18/00 have been fully considered but they are not persuasive.

Applicants argue that the present invention makes no claim in any way to the issues of gene therapy, such as vector design, gene delivery and gene expression, as well gene therapy being unpredictable and unsuccessful. Claims may not specifically recite gene therapy, but the claims fail to recite any context and therefore read on *in vitro* as well as *in vivo*(whole organism), and thus embrace gene therapy.

Additionally, on page 2 of the specification, lines 1-5, applicant asserts that the present invention relates generally to the fields of gene therapy. . . . . that the present invention relates to an adenoviral vector encoding an pro-apoptotic bax gene for gene therapy. Furthermore, on page 4 of the specification, applicant states that since the prior art is deficient in the lack of effective means of gene therapy using adenoviral vector encoding a pro-apoptotic bax gene, the present invention fulfils a longstanding need and desire in the art. Thus, applicants have expressly contemplated *in vivo* applicability and gene therapy in one aspect of the invention, a limitation which can be read into the broad claim since its scope embraces *in vivo* applicability.

In addition, applicants argue that the present invention is drawn to the induction of apoptosis and inhibition of cell growth by inducible expression of the Bax gene, wherein the expression of the Bax gene leads to apoptosis and sensitization to chemotherapy and/or radiotherapy. Therefore, as applicants recognize in their arguments that they intend for the broad scope of the claims to encompass *in vivo* applicability, since they reference the invention to induce apoptosis in conjunction with chemotherapy, where chemotherapy is an *in vivo* procedure.

Applicants argues that *in vitro* studies are accepted by those with ordinary skill in the art as being predictive of success *in vivo*, and that the present specification discloses efficacy of the inducible Bax gene expression *in vitro* which enables the use of the compounds *in vivo*. However, this was not found persuasive. For certain fact patterns, it is true that *in vitro* studies are representative of *in vivo* studies. However, where the therapeutic is observed *in vivo* via recombinant means, the art is highly unpredictable and *in vitro* success rarely correlates with being able to deliver and treat *in vivo* successfully. See the art cited in support by Crystal, R. G, Science, 270, 404-410, 1995. Applicants provide no evidence of a correlation for the instant invention, that *in vitro* results would provide any expectation of similar delivery *in vivo*.

Applicants argue that the examiner cites no case law to support the enablement rejection. The examiner is unaware of any requirement that case law *per se* be cited to support any rejection during patent prosecution. However, note that the enablement rejection previously set forth followed the analysis supported by *In re Wands*, 858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir., 1988), to establish that it would require undue experimentation to practice the invention as claimed in view of the applicants disclosure and the state of the art at the time of filing. See the enablement rejection previously set forth citing such an analysis. Note however *In re Wands* was not explicitly cited.

Further, no case law need be cited by the examiner in support of the instant enablement rejection. The previous rejection properly indicated that it would require undue experimentation to practice the invention as claimed drawn, to *in vivo* applicability. It remains that applicants have

failed to establish how the *in vitro* example would enable *in vivo* success in view of the known unpredictability in the art and lack of guidance in that regard for the specific invention as claimed. Again, in the gene therapy art, *in vitro* successes are not regarded as correlative of *in vivo* successes, since issues regarding delivery and expression become highly unpredictable for the reasons cited previously compared to transducing cells *in vitro* and obtaining an effect.

Applicant's citation of *Cross v Iizuka* is not considered on point here since that decision is not generally applicable to every type of therapy *per se*. The fact in *Cross v Iizuka* had nothing to do with gene therapy or assessment of the gene therapy technology, therefore, it is unclear how this decision correlates to gene therapy.

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. No disease was successfully treated using rAV vector gene therapy. This is reflected by several subsequently published reviews, at least one of which is mentioned. W. French Anderson (Nature 392 S, 25-30, 1998) teaches that: "the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how *in vivo* immune defenses can be overcome, and how to manufacture efficiently the vectors that we do make".

Breadth of the claims. The claims are extremely broad, encompassing treatment of any and all individuals having a pathophysiological state. Applicant is proposing to treat several

neoplastic diseases, notably ovarian cancer, by administering a pharmacologically effective dose of recombinant adenoviral vector encoding a pro-apoptotic bax gene.

Working examples. No working example is disclosed in the specification of the claimed invention which would enable the invention as claimed. While the specification provides excellent *in vitro* examples and impressive results based on these *in vitro* experiments, it fails to give sufficient evidence for the *in vivo* treatment encompassing administering a recombinant adenoviral vector encoding pro-apoptotic bax gene and the ensuing results. The one *in vivo* example given does not enable the invention since the nude mice were given ovarian cancer cells already pre-treated with the recombinant adenoviral vector encoding the bax gene, after which the mice were irradiated. It may have been more instructive to administer the ovarian cancer cells in vivo, wait until a tumor was established, then administer a therapeutically effective dose of the recombinant adenoviral vector encoding the bax gene and compare with irradiation before, during or after vector therapy. The *in vivo* example as listed pre-supposes that an individual would be subjected to *ex*-vivo gene therapy, and if this is the nature of the invention, then the specification as disclosed was misleading.

While the specification discloses a mammalian patient, preferably a human patient, the applicant must remember that: humans are not simply large mice. Studies in experimental animals may not necessarily predict the toxicology of vectors in humans. Crystal, R. G; Science 270, 404-410 (1995). As noted in a recent review by the NIH report on gene therapy: although animal

investigations are often invaluable, it is not always possible to extrapolate directly from animal experiments to human studies.

Guidance in the specification. The specification fails to provide an enabling disclosure because it fails to provide adequate guidance that would have been accepted by the artisan in regard to the efficacious delivery of useful genes for treatment of any human disorder. It is incumbent upon applicants to provide sufficient and adequate teachings present within the specification for such therapeutic regimens. The specification fails to provide therapeutic routes of vector administration. While it is noted that in the mouse test system, ex-vivo vector therapy resulted in the alteration of an immune response, no indication is present that such a system has any clinical correlate. Thus the teachings and guidance present in the specification as a whole represent an initial investigation into the feasibility of the development of a useful means of executing gene therapy which awaits development to the practical level.

In the application, applicants have not taught that neoplastic diseases can be effectively treated by using the claimed vector. Given the highly unpredictable nature of both the in vivo regulation of gene expression in general and modulation of immune response in particular, in the absence of appropriate and specific guidance, the practitioner would have been required to have exercised a vast amount of experimentation in the practice of the full scope of what is claimed. For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

No claims are allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvette Connell, whose telephone number is 703-308-7942. The examiner can normally by reached on Monday-Friday from 7:30 to 4:00(Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on 703-308-0447.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Yvette Connell

June 22, 2000

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600